GOOD EVIDENCE MATTERS

GEMs of the Week

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Can We Medicate the Migraine Monster?

Preventive Medications in Pediatric Migraine: A Network Meta-Analysis

Kohandel Gargari O, Aghajanian S, Togha M, et al. Preventive Medications in Pediatric Migraine: A Network Meta-Analysis. *JAMA Netw Open*. 2024;7(10):e2438666. Published 2024 Oct 1. doi:10.1001/jamanetworkopen.2024.38666

KEY TAKEAWAY: Medications such as topiramate and pregabalin decrease migraine frequency in pediatric patients diagnosed with migraines with or without aura.

STUDY DESIGN: Meta-analysis of 45 randomized controlled trials (RCTs) (N=3,771)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Migraines are a common neurologic disorder in the pediatric population and increase in prevalence after puberty. Migraines can affect all aspects of a child's life including personal, academic, and emotional. There are multiple treatment modalities for migraines and this meta-analysis aimed to look at which pharmacologic agents are the most effective in their ability to decrease frequency of migraine in the pediatric population.

PATIENTS: Pediatric patients diagnosed with migraines with or without aura

INTERVENTION: Oral pharmacologic medications

CONTROL: Placebo

PRIMARY OUTCOME: Headache frequency

Secondary Outcome: 50% reduction rate, headache duration, quality of life and disability produced by migraines, headache intensity, risk of medication adverse effects

METHODS (BRIEF DESCRIPTION):

- PubMed, Embase, SCOPUS, and ClinicalTrials.gov were searched to select articles for inclusion.
- Trials that included patients ≤18 years old who suffered from migraines with or without auras, study effects of pharmacological drugs effects of migraines, and looked at outcomes of headache frequency, ≥50 responder rate, headache duration, headache intensity, and study time of randomized clinical trials were included in the study.
- Trials that had patients >18 years old, non-pharmacologic treatments, and non-randomized control trials were excluded from the study.
- Intervention groups received pregabalin topiramate, topiramate with vitamin D3, flunarizine, levetiracetam, riboflavin, cinnarizine, propranolol, trazadone, melatonin, pizotifen, vitamin B complex, Coenzyme Q10, carnitine, 5HTP, nimodipine, butterbur root extract and amitriptyline
  - Doses/frequency ranged significantly between studies.
- The control group received a placebo.
- The primary outcome measured headache frequency after treatment, defined as the number of migraines per month.
- Secondary outcomes consisted of the following:
  - ≥50% responder rate was defined as number of patients with at least 50% decrease in headache frequency after treatment compared to baseline
  - Headache duration was defined as how long the migraine last in hours.
  - Quality of Life and Disability produced by migraine was measured by the PedMIDAS tool, a six-question tool developed to assess the disability caused by migraines in school-age children and adolescent. Higher scores indicate worse quality of life and severe disability.
  - Headache intensity was measured on a scale from 0–10, with a score of 10 representing the most intense headache.
  - Risk of adverse events were defined as specific adverse events not stated in study or supplemental data.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Pregabalin, topiramate with vitamin D3, flunarizine, levetiracetam, riboflavin, cinnarizine, topiramate, and amitriptyline showed a significant decrease in headache frequency compared to placebo.
  - Pregabalin (ratio of means [RoM] 0.38; 95% CI, 0.18–0.79)

- Topiramate with vitamin D3 (RoM 0.44; 95% CI, 0.30–0.65)
- Flunarizine (RoM 0.46; 95% CI, 0.26–0.81)
- Levetiracetam (RoM 0.47; 95% CI, 0.30–0.72)
- Riboflavin (RoM 0.50; 95% CI, 0.32–0.77)
- Cinnarizine (RoM 0.64; 95% CI, 0.46–0.88)
- Topiramate (RoM 0.70; 95% CI, 0.55–0.89)
- Amitriptyline (RoM 0.73; 95% CI, 0.54–0.97)

Secondary Outcome –

- Flunarizine and alpha-lipoic acid, flunarizine, pregabalin, and cinnarizine reduced headache frequency by ≥50% compared to placebo.
  - Flunarizine and α-lipoic acid (risk ratio [RR] 8.7; 95% CI, 2.4–31)
  - Flunarizine (RR 4.0; 95% CI, 1.4–12)
  - Pregabalin (RR 1.9; 95% CI, 1.1–3.1)
  - Cinnarizine (RR 1.5; 95% CI, 1.0–2.1)
- Propranolol and cinnarizine, valproate, levetiracetam, and cinnarizine alone showed a significant decrease in headache intensity compared to placebo.
  - Propranolol and cinnarizine (RoM 0.45; 95% CI, 0.28–0.72)
  - Pregabalin (RoM 0.57; 95% CI, 0.33–0.96)
  - Valproate (RoM 0.60; 95% CI, 0.49–0.72)
  - Levetiracetam (RoM 0.62; 95% CI, 0.50–0.77)
  - Cinnarizine (RoM 0.64; 95% CI, 0.54–0.76)
- None of the treatments showed a significant effect on the quality of life and disability produced by migraines.
- None of the treatments showed a significant decrease in duration of headaches.
- Amitriptyline, topiramate, and valproate had a higher chance of adverse events when compared to placebo:
  - Amitriptyline (RR 3.8; 95% CI, 1.4–10)
  - Topiramate (RR 4.3; 95% CI, 1.6–12)
  - Valproate (RR 5.9; 95% CI, 1.9–18)

LIMITATIONS:

- Study size of the individual studies was small, leading to great bias.
- Multiple studies were from Iran contributing to a bias in population studied.
- Certain medications (levetiracetam, cinnarizine, and flunarizine) were included in limited studies so the results were limited by population size and number of studies.

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Beyond Blood Sugar: Metformin for Aching Knees in Obesity

Metformin as Adjuvant Therapy in Obese Knee Osteoarthritis Patients

Aiad AAE, El-Haggar SM, El-Barbary AM, El-Afify DR. Metformin as adjuvant therapy in obese knee osteoarthritis patients. *Inflammopharmacology*. 2024;32(4):2349-2359. doi:10.1007/s10787-024-01495-y

KEY TAKEAWAY: Metformin as an adjuvant therapy with celecoxib improves pain, stiffness, and function compared to celecoxib alone in obese adults with knee osteoarthritis (OA).

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Knee OA is a prevalent cause of disability, particularly in obese individuals. Metformin, known for its anti-inflammatory and metabolic effects, may offer additional benefits in OA management as adjuvant therapy with non-steroidal anti-inflammatory drugs (NSAIDs). This study aimed to investigate whether metformin combined with celecoxib improves pain, stiffness, and function in obese patients with knee OA.

PATIENTS: Obese adults ≥45 years old with radiologically confirmed knee OA

INTERVENTION: Metformin + celecoxib

CONTROL: Placebo + celecoxib

PRIMARY OUTCOME: Pain, stiffness, and function

Secondary Outcome: Inflammatory markers

METHODS (BRIEF DESCRIPTION):

- Individuals ≥45 years old with a body mass index (BMI) ≥30, and symptomatic with radiographic confirmation of knee OA were included in the study.
- The study excluded individuals with autoimmune disease, diabetes, hypertension, cancer, or prior steroid injections
- Patients were randomized 1:1 to either:
  - Metformin 500 mg twice daily + celecoxib 200 mg daily
  - Placebo twice daily + celecoxib 200 mg daily
- Patients were instructed to maintain a standardized diet and activity level.
- The primary outcome measured pain, stiffness, and function via the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Scores range from 0–96, with higher scores indicating worse symptoms.
- The secondary outcome evaluated serum biomarkers COMP, CTX-1, IL-1β which were measured via ELISA.

INTERVENTION (# IN THE GROUP): 25

COMPARISON (# IN THE GROUP): 25

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Metformin significantly reduced the composite of pain, stiffness and function (mean score 40 vs 54, respectively; $p<.0001$)
- Metformin significantly reduced pain compared to placebo (mean score 7.7 vs 10, respectively; $p<.0001$).
- Metformin significantly reduced stiffness compared to placebo (mean score 3.7 vs 5.0, respectively; $p<.0001$).
- Metformin significantly improved function compared to placebo (mean score 29 vs 39, respectively; $p<.0001$).

Secondary Outcome –

- Metformin significantly decreased the following inflammatory markers compared to placebo:
  - Serum COMP (900 vs 1,300 ng/mL, respectively; $p=.0081$)
  - Serum CTX-1 (10 vs 13 ng/mL, respectively; $p=.0106$)
  - Serum IL-1β (1,900 vs 2,400 pg/mL, respectively; $p=.02$)

LIMITATIONS:

- The study had a small sample size of only 50 participants, which potentially limits statistical power.
- The study was conducted at a single center in Egypt, which may affect applicability to more diverse populations.
- The follow-up period was limited to 12 weeks, which makes it unclear whether the observed

benefits of metformin lead to long term improvement.

- Dietary and physical activity adherence was self-reported, which can lead to recall or reporting bias.

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Time is of The Essence: Is Negative Pressure Wound Therapy Superior?

Negative Pressure Wound Therapy vs Usual Care in Patients with Surgical Wound Healing by Secondary Intention in The UK (SWHSI-2): An Open-Label, Multicenter, Parallel-group, Randomized Controlled Trial

Arundel C, Mandefield L, Fairhurst C, et al. Negative Pressure Wound Therapy Versus Usual Care in Patients with Surgical Wound Healing by Secondary Intention in The UK (SWHSI-2): An Open-Label, Multicenter, Parallel-group, Randomized Controlled Trial. *Lancet*. 2025;405(10490):1689-1699. doi:10.1016/S0140-6736(25)00143-6

KEY TAKEAWAY: There is no significant benefit of treatment with negative pressure wound therapy (NPWT) compared to standard wound therapy for patients with surgical wounds healing by secondary intention (SWHSI).

STUDY DESIGN: Multicenter, parallel group randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: NPWT is commonly used to promote this type of healing, but there is limited research supporting the superiority of treatment. This study aimed to determine if NPWT improves healing time compared to standard wound therapy.

PATIENTS: Adults with SWHSI

INTERVENTION: NPWT

CONTROL: Standard wound therapy

PRIMARY OUTCOME: Healing time

Secondary Outcome: Incidence of hospital admission, infection, repeat surgery, amputation, wound infection, antibiotic use, death

METHODS (BRIEF DESCRIPTION):

- Patients ≥16 years old (median age 63 years old) with an acute (<6 weeks post-surgery) post-surgical wound healing by secondary intention were included in the study.
- Patients with malnourishment, <6-month life expectancy, active systemic infection, chronic or non-surgical wounds, bleeding concerns, or treatment contraindications were excluded from the study.
- Patients were randomized 1:1 to receive NPWT or standard wound therapy.
- Patients in the intervention group received NPWT in accordance with manufacturer guidance.
- Patients in the control group received routine wound therapy per clinician's preference.
- The primary outcome was measured in days until complete epithelial cover in absence of a scab.
- The secondary outcomes assessed the incidence of hospital admission, infection, repeat surgery, amputation, wound infection, antibiotic use, or death and was measured by the rate of occurrence.

INTERVENTION (# IN THE GROUP): 349

COMPARISON (# IN THE GROUP): 337

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- NPWT did not significantly reduce healing time compared to standard therapy (hazard ratio [HR] 1.1; 95% CI, 0.88–1.3).

Secondary Outcome –

- There was no significant difference with NPWT in hospital admission, re-operation rate, amputation, wound infection, antibiotic use, or death compared to standard therapy.

LIMITATIONS:

- There was an overrepresentation of patients with lower extremity wounds and diabetes.
- The study design limited consistent recruitment of patients from specialty surgical services.
- The study allowed for treatment variations based on clinician preference in the control group.

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